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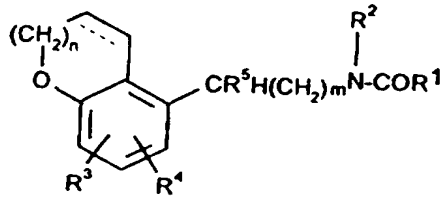
(54) Title: BENZOFURANS AND BENZOPYRANS AS CHRONOBIOLOGICAL AGENTS

(57) Abstract

A compound of formula (I), wherein R^1 and R^2 which may be the same or different represent H, C_{1-6} alkyl, C_{3-7} cycloalkyl or aryl; R^3, and R^4 which may be the same or different represent H, halogen, C_{1-6} alkyl; or substituted aryl; R^5 represents H or C_{1-6} alkyl or; n is an integer 0, 1 or 2 and m is an integer 1, 2, 3 or 4; the dotted line indicates the presence or absence of an additional bond; and pharmaceutically acceptable solvates thereof.



(I)

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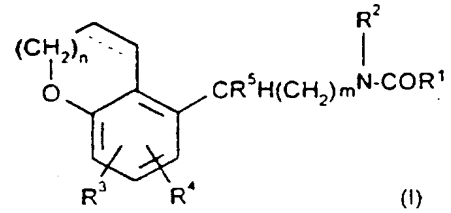
BENZOFURANS AND BENZOPYRANS AS CHRONOBIOLOGICAL AGENTS

This invention relates to bicyclic compounds, to processes for their preparation, to pharmaceutical compositions containing them and to their medical use.

The invention thus provides compounds of Formula (I)



(I)

wherein R^1 and R^2 which may be the same or different represent H, C_{1-6} alkyl or substituted alkyl or C_{3-7} cycloalkyl; or aryl;

R^3, and R^4 which may be the same or different represent H, halogen, C_{1-6} alkyl; or substituted aryl;

R^5 is H or C_{1-6} alkyl;

n is an integer 0, or 1

and m is an integer 1, 2, 3, or 4;

the dotted line indicates the presence or absence of an additional bond;

and pharmaceutically acceptable solvates (e.g. hydrates) thereof.

It will be appreciated that in formula (I) hereinabove the substituents R^3 and R^4 may be attached at any available position on the phenyl portion of the bicyclic system. Preferably when n is 0, R^3 and R^4 are substituted in the 5 and/or 7 positions on the phenyl ring.

As used herein, an alkyl group may be a straight chain or branched chain alkyl group. Examples of suitable alkyl groups include C_{1-4} alkyl groups, for example methyl, ethyl, n-propyl and isopropyl groups. When optionally substituted, the substituent is one or more fluorine atoms.

A halogen substituent may be fluorine, chlorine, bromine or iodine.

As used herein, the term "aryl" as a group means phenyl, optionally substituted by one or more (eg 1-3) atoms or groups selected from C_{1-6} alkyl, C_{1-6} alkoxy, hydroxyl, halogen, nitro and trifluoromethyl.

Cycloalkyl groups may be bridged cycloalkyl groups, eg norbornyl or non-bridged cycloalkyl groups, eg cyclopropyl.

Examples of the groups R3 and R^4 include hydrogen, halogen (e.g. chlorine and/or fluorine) and C_{1-3}alkyl (e.g. methyl).

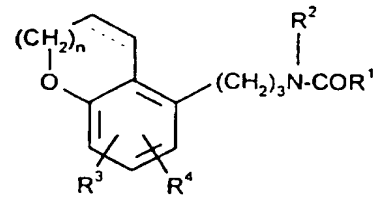
m preferably represents 2.

n preferably represents 0.

R2 may particularly represent hydrogen or C_{1-3}alkyl (e.g. methyl).

R1 may particularly represent hydrogen, C_{1-3}alkyl (i.e. methyl, ethyl, n-propyl or i-propyl) or C_{3-5}cycloalkyl (e.g. cyclopropyl or cyclobutyl).

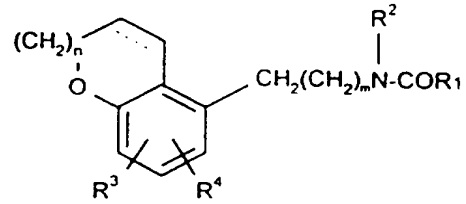
A particular group of compounds of the invention are compounds of formula (1a).



(1a)

and pharmaceutically acceptable solvates (e.g. hydrates) thereof, wherein R^1, R^3, and R^4 are as defined hereinabove especially halogen, more especially R^3 and R^4 are chlorine and/or fluorine, especially where R^1 is methyl or cyclopropyl.

Another particular group of compounds of the invention are compounds of formula 1(b)



(1b)

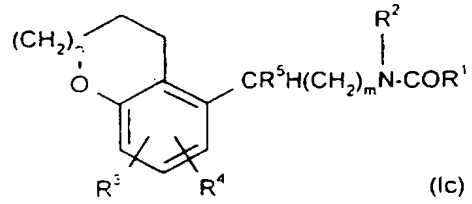
wherein R^1 and R^2 which may be the same or different represent H, C_{1-6} alkyl or substituted alkyl, C_{3-7} cycloalkyl or aryl;

R^3, and R^4 which may be the same or different represent H, halogen, C_{1-6} alkyl or substituted aryl;

n is an integer 0, or 1

and m is an integer 1, 2, 3, or 4;
the dotted line indicates the presence or absence of an additional bond;
and pharmaceutically acceptable solvates (e.g. hydrates) thereof.

A further particular group of compounds are compounds of formula 1(c)



(Ic)

wherein R^1 and R^2 which may be the same or different represent H, C_{1-6} alkyl or C_{3-7} cycloalkyl;
R^3, and R^4 which may be the same or different represent H, halogen, or C_{1-6} alkyl;
R^5 is H or C_{1-6} alkyl;
n is an integer 0, or 1
and m is an integer 1, 2, 3, or 4;
the dotted line indicates the presence or absence of an additional bond;
and pharmaceutically acceptable solvates (e.g. hydrates) thereof.

Particular compounds according to the present invention include
N-[3-(2,3-dihydro-benzofuran-4-yl)-propyl]acetamide,
Cyclopropanecarboxylic acid -[3-(2,3-dihydro-benzofuran-4-yl)-propyl]-amide,
Cyclopropanecarboxylic acid -[3-(5-chloro-2,3-dihydro-benzofuran-4-yl)propyl]amide,
Cyclopropanecarboxylic acid -[3-(5-chloro-7-fluoro-2,3-dihydro-benzofuran-4-yl)propyl]-amide,
Cyclopropanecarboxylic acid [3-(5-chloro-7-fluoro-benzofuran-4-yl)-propyl]-amide,
Cyclopropanecarboxylic acid -[3-benzofuran-4-yl)-propyl]-amide,
Cyclopropanecarboxylic acid (3-chroman-5-yl-propyl)-amide,
N-[3-(2,3-dihydro-5-fluorobenzofuran-4-yl)propyl]acetamide,
Cyclopropanecarboxylic acid [3-(2,3-dihydro-5-fluoro-benzofuran-4-yl)propyl]amide.

It is to be understood that the present invention covers all combinations of particular and preferred groups described hereinabove.

References hereinafter to a compound of formula (I) includes the compound and its pharmaceutically acceptable solvates.

The compounds of formula (I) may contain at least one asymmetric carbon atom and may exist as stereoisomers. The compounds of formula (I) thus include the R- and S-isomers and mixtures, for example racemic mixtures, thereof.

The compounds of formula (I) have a high affinity and selectivity for binding to melatonin receptors and have either melatonin agonist or antagonist activity as demonstrated in cloned human ML1 receptors in Chinese hamster ovary cells. Accordingly, the compounds are of use as scientific tools for studying the role of melatonin within biological systems.

The compounds of formula (I) are also of use in the treatment of disorders which arise from a disturbed functioning of systems which are regulated by melatonin. In particular the compounds of formula (I) may be used in the treatment of chronobiological disorders, especially in the elderly population, glaucoma, cancer, psychiatric disorders, neurodegenerative diseases or neuroendocrine disorders arising as a result of or influenced by the systems which are regulated by melatonin.

Chronobiological disorders include seasonal affective disorders (SAD), primary and secondary insomnia disorders, primary and secondary hypersomnia disorders, sleep-wake schedule disorders (including advanced phase type, delayed phase type, disorganised type and frequently-changing type) and other dyssomnias, especially those caused by ageing, dementias, blindness, shift work and by rapid time-zone travel, commonly known as jet lag.

Cancers which may be treated with a compound of formula (I) include solid tumours, e.g. melanomas and breast carcinomas.

Psychiatric disorders which may be related to altered melatonin function or influenced by melatonin and circadian rhythms include mood disorders (including bipolar disorders of all types, major depression, dysthymia and other depressive disorders), psychoactive substance dependence and abuse, anxiety disorders (including panic disorder, agoraphobia, social phobia, simple phobia, obsessive-compulsive disorder, post-traumatic stress disorder and generalised anxiety disorder), schizophrenia, epilepsy and epileptic seizures (including grand

mal, petit mal, myoclonic epilepsy and partial seizures), disorders of involuntary movement (including those due to Parkinson's disease, and drug-induced involuntary movements) and dementias (including primary degenerative dementia of the Alzheimer type).

Neurodegenerative diseases which may be related to altered melatonin function or influenced by melatonin and biological rhythms include multiple sclerosis and stroke.

Neuroendocrine disorders which may be related to altered melatonin function or influenced by melatonin and biological rhythms include peptic ulceration, emesis, psoriasis, benign prostatic hyperplasia, hair condition and body weight. Particular neuroendocrine disorders which may be treated include those relating to the regulation of reproductive maturation and function include idiopathic delayed puberty, sudden infant death, premature labour, infertility, antifertility, premenstrual syndrome (including late luteal phase dysphoric disorder) and sexual dysfunction (including sexual desire disorders, male erectile disorder, post-menopausal disorders and orgasm disorders). The compounds may also be used to manipulate breeding cycles, body weight, coat colour and oviposition of susceptible hosts, including birds, insects and mammals. The compounds of formula (I) may also have sedative and analgesic effects, effects on the microcirculation and immunomodulant effects and may be useful for the treatment of hypertension, migraine, cluster headache, regulation of appetite and in the treatment of eating disorders such as obesity, anorexia nervosa and bulimia nervosa.

There is thus provided in a further aspect of the invention a compound of formula (I) for use in therapy, in particular in human medicine. It will be appreciated that use in therapy embraces but is not necessarily limited to use of a compound of formula (I) as an active therapeutic substance.

There is also provided as another aspect of the invention a compound of formula (I) for use in the preparation of a medicament for use in the treatment of conditions associated with a disturbed functioning of the melatonin system.

In an alternative or further aspect of the invention there is provided a method for the treatment of a mammal, including man, comprising administration of an effective amount of a compound of formula (I), in particular for the treatment of conditions associated with a disturbed functioning of the melatonin system.

It will be appreciated by those skilled in the art that reference herein to therapy and treatment extends to prophylaxis as well as the treatment of established symptoms.

While it is possible that, for use in therapy, a compound of formula (I) may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides a pharmaceutical formulation comprising a compound of formula (I) together with one or more pharmaceutically acceptable carriers therefor. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, vaginal, nasal, topical or parenteral (including intramuscular, subcutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active compound with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or

acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid).

For topical administration in the mouth, the compositions may take the form of buccal or sub-lingual tablets, drops or lozenges formulated in conventional manner.

For topical administration to the epidermis the compounds may be formulated as creams, gels, ointments or lotions or as a transdermal patch. Such compositions may for example be formulated with an aqueous or oily base with the addition of suitable thickening, gelling, emulsifying, stabilising, dispersing, suspending and/or colouring agents.

The compounds of the invention may be formulated for parenteral administration by injection, conveniently intravenous, intramuscular or subcutaneous injection, for example by bolus injection or continuous intravenous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glyceride.

Pessaries for vaginal administration may be formulated in a similar manner.

For intranasal administration the compounds of the invention may be used, for example, as a liquid spray, as a powder or in the form of drops.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. 1,1,1,2-trifluoroethane (HFA 134A) and 1,1,1,2,3,3,3 - heptafluoropropane (HFA 227), carbon dioxide or other suitable gas. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

Any of the pharmaceutical compositions described above may be presented in a conventional manner associated with controlled release forms.

The active ingredient may conveniently be presented in unit dose form. A convenient unit dose formulation contains the active ingredient in an amount of from about 0.1mg to about 200mg.

It will be appreciated that the precise dose administered will depend on the age and condition of the patient, the particular compound used and the frequency and route of administration and will ultimately be at the discretion of the attendant physician. The compound may be administered in single or divided doses and may be administered one or more times, for example 1 to 4 times per day.

A proposed dose of the compounds of the invention for oral, rectal, vaginal, intranasal, topical or parenteral administration to humans (of approximately 70kg bodyweight) for the treatment of conditions associated with a disturbed functioning of systems which are regulated by melatonin is 0.01 to 200mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

For oral administration a unit dose will preferably contain from 0.1 to 200mg of the active ingredient. A unit dose for parenteral administration will preferably contain 0.1 to 5 mg of the active ingredient.

Aerosol formulations are preferably arranged so that each metered dose or 'puff' delivered from a pressurised aerosol contains 0.2 mg to 2 mg of a compound of the invention, and capsules and cartridges delivered from an insufflator or an inhaler, contain 0.2 mg to 20 mg of a compound of the invention. The overall daily dose by inhalation with an aerosol will be within the range 0.2 mg to 100 mg. Administration may be once or several times daily, for example from 1 to 8 times, giving for example 1, 2 or 3 doses each time.

Dosages of the compounds of the invention for rectal, vaginal, intranasal or topical administration are similar to those for oral administration.

The compounds of the invention may, if desired, be administered in combination with one or more other therapeutic agents such as a hypnotic or antidepressant agent, or an anti-cancer agent such as tamoxiphen, or in combination with radiation therapy to treat cancer.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical

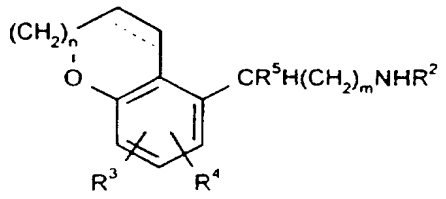
formulations comprising a compound of formula (I) together with at least one other therapeutic agent and one or more pharmaceutically acceptable carriers therefore comprise a further aspect of the invention.

When compounds of formula (I) are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

When such combinations are employed, the dose of each component of the combination will in general be that employed for each component when used alone.

Compounds of formula (I) and pharmaceutically acceptable solvates (e.g. hydrates) thereof, may be prepared by methods known in the art for the preparation of analogous compounds. In particular the compounds of formula (I) may be prepared by the methods outlined below and which form a further aspect of the invention. In the following processes, R^1, R^2, R^3, R^4, R^5 n and m unless stated otherwise, are as defined above for formula (I).

According to one general process (A) a compound of formula (I) may be prepared by acylation of a compound of formula (II),



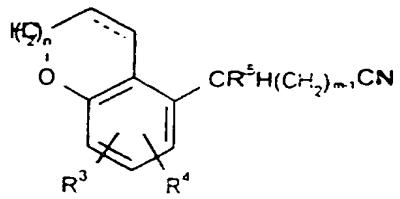
(II)

Suitable acylating agents which may conveniently be used in the above process include acid anhydrides and acid halides. The reaction is conveniently effected in a suitable solvent such as an ether (e.g. diethyl ether, tetrahydrofuran or dioxan), a hydrocarbon such as toluene or a halogenated hydrocarbon (e.g. dichloromethane), esters (e.g. ethylacetate) preferably in the presence of a base such as pyridine or a tertiary amine (e.g. triethylamine), at a temperature in the range of 0 to 100°C, preferably 0 to 20°C.

The compounds of formula (I) thus produced wherein the dotted line represents an extra bond may be converted into the corresponding compound wherein the dotted line does not represent an extra bond by hydrogenation, for example hydrogenating the compound in ethanol over a transition metal catalyst

eg rhodium which is then removed eg by filtration and the compound then subjected to further purification techniques.

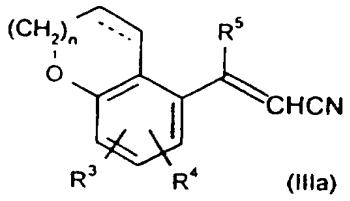
Compounds of formula (II) in which R^2 is hydrogen and the dotted line represents a bond may conveniently be prepared by the reduction of compounds of formula (III).



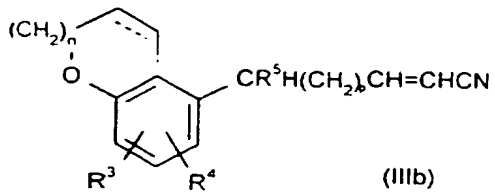
(III)

The reduction may conveniently be effected using a reducing agent such as borane in an ether solvent (e.g. tetrahydrofuran) optionally in the presence of a suitable acid (e.g. trifluoroacetic acid, hydrochloric acid or the like), and heating the reaction mixture to reflux for about 3 to 5 hours. Alternatively, the reduction may employ catalytic hyrogenation in the presence of a noble metal catalyst, such as platinum, palladium or the like, in a suitable organic solvent, such as an alcoholic solvent, e.g. ethanol, conveniently at a temperature in the range of 0° to 100°C, aptly at room temperature.

Alternatively, compounds of formula (IIIa) and (IIIb) in which p=0,1



(IIIa)



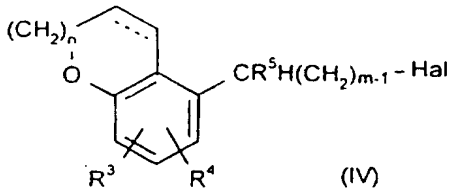
(IIIb)

may be converted to the compound of formula (II) in which R^2 is hydrogen and m is 2,3 or 4 by hydrogenation preferably in a suitable solvent such as acetic acid in the presence of for example, palladium on charcoal with platinum and / or rhodium on charcoal. This process is carried out at a pressure of 50-180psi, peferably 50-110 psi and more preferably 70-100psi a temperature in the range 30-100°C, preferably 30-80°C, more preferably 50°C for a sufficient time period normally 24 hours.

Conveniently compounds (IIIb) may be converted directly into compounds (I) by carrying out this hydrogenation in the presence of an acid anhydride. The temperature and pressure may be adjusted to determine the degree of halogenation and unsaturation in the final product.

Compounds of formula (II) in which R^2 is C_{1-6} alkyl may be prepared by N-alkylation of compounds of formula (II) in which R^2 is hydrogen using standard procedures.

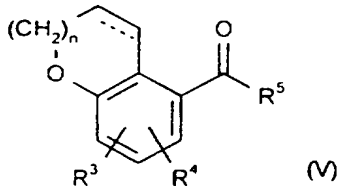
Compounds of formula (III) may be prepared from the following compounds of formula (IV)



(IV)

wherein Hal represents one of the halide groups eg, chloride, bromide or iodide. The preparation involves reaction with an alkali metal cyanide such as potassium cyanide and the like, suitably in the presence of an alcoholic solvent.

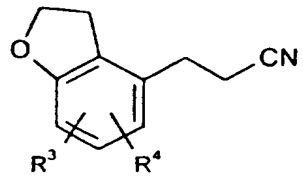
Compounds of formula (IIIa) and (IIIb) may be prepared from compounds of formula (V)



(V)

where R^5 = H or C_{1-6} alkyl. The preparation may conveniently be conducted using Wittig or Horner-Emmons type chemistry ie using a dialkyl cyanoalkyl phosphonate eg diethyl cyanomethyl phosphonate in the presence of a strong base eg sodium hydride in a suitable solvent eg THF.

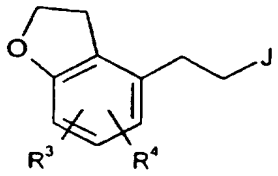
In a particularly preferred embodiment of Route A Compounds of formula (II) where m is 2, n is zero, R^5 is H, and the dotted line does not represent a bond, (i.e. the 5 membered ring is saturated) may alternatively be prepared from compounds of formula (VI)



(VI)

by for example treatment heating under reflux with borane in tetrahydrofuran.

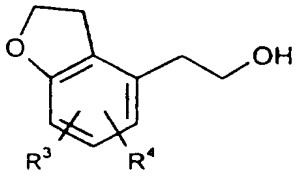
Compounds of formula (VI) may be prepared from a compound of formula (VII)



(VII)

wherein J represents a suitable leaving group, for example a mesylate group, a tosyl group or halogen by treatment with an organic cyanide, for example sodium cyanide.

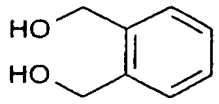
Compounds of formula (VII) may be prepared from compounds of formula (VIII)



(VIII)

by reaction with suitable activating reagents, for example, methane sulfonyl chloride, tosyl chloride or a halogenating agent.

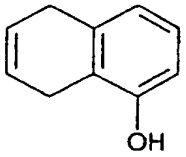
Compounds of formula (VIII) may be prepared from compounds of formula (IX).



(IX)

by reaction with suitable acids, e.g. hydrochloride acid. If required, the substituents R^3 and/or R^4 (wherein R^3 and/or R^4 are both halogens) can be introduced into structure (VIII) with suitable reagents (e.g. N-bromosuccinimide if R^3 and/or R^4 is bromine or N-chlorosuccinimide if R^3 and/or R^4 is chlorine).

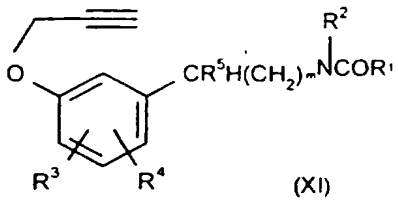
The compounds of formula (IX) may be prepared from the compound of formula (X)



(X)

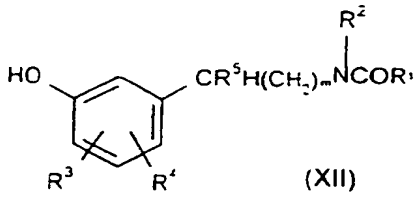
by ozonolysis. The compound of formula (X) is commercially available, or may be prepared by Birch reduction from the corresponding naphthol. At any stage in this process, compounds in which R3 and/or R4 are H or halogen may be modified into compounds in which R3 and/or R4 represent halogen, C1-6 alkyl or substituted aryl using reactions that would be apparent to a skilled person.

According to a further process (B), a compound of formula (I) where n=1 may be prepared by cyclisation of a compound of formula (XI)



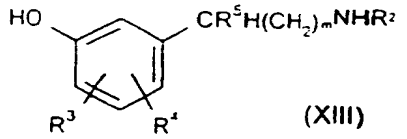
(XI)

The cyclisation is conveniently affected by heating in a suitable high boiling solvent (eg bromobenzene, N,N-diethylaniline). Compounds of formula (XI) may be prepared by alkylation of a compound of a compound of formula (XII)



(XII)

using a propargyl halide (eg propargyl bromide) in the presence of a base such as potassium carbonate in a suitable solvent (eg DMF). Compounds of formula (XII) may be prepared by acylation of a compound of formula (XIII)

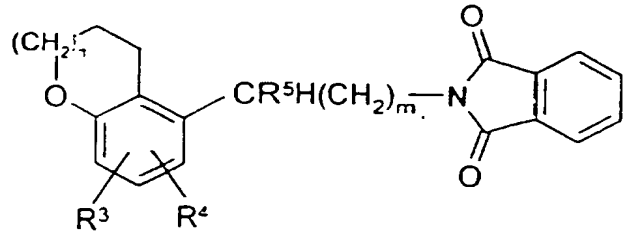


(XIII)

Suitable acylating agents and conditions which may conveniently be used in this process include those previously described for acylation of compounds of formula (II).

It will be appreciated that compounds of formulae (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (XI), (XII) and (XIII) and (XIV) - (XVIII) below are novel intermediates and represent further individual aspects of the present invention.

According to a further Process (C), the compounds of formula (I) in which R^2 = H and in which m = 2, 3, or 4 may be prepared from compounds of formula

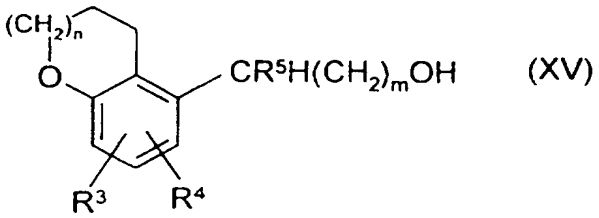


(XIV)

(XIV)

by treatment with a primary amine such as methylamine or hydrazine followed by acylation following the procedures described in Process (A).

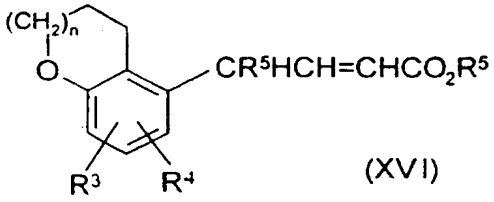
Compounds of formula (XIV) may be prepared from alcohols of formula (XV)



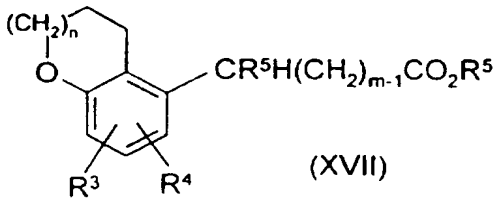
(XV)

by reaction with phthalimide under Mitsunobu conditions using for example triphenyl phosphine and diethyl azodicarboxylate in a suitable solvent such as tetrahydrofuran.

The alcohols of formula (XV) may be prepared by a number of methods apparent to the skilled person such as by reduction of acids or esters of formulae (XVI) or (XVII)



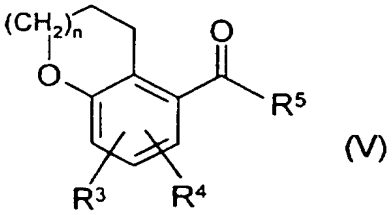
(XVI)



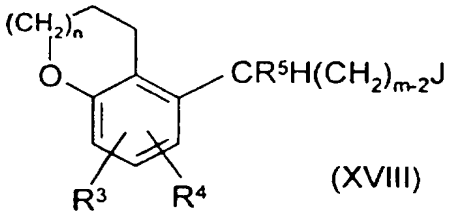
(XVII)

using for example lithium aluminium hydride in a suitable solvent such as tetrahydrofuran.

Such esters (XVI) and (XVII) are readily obtained using standard reactions. For example (XVI) may be prepared from aldehydes or ketones (V) via Wittig type reactions, or (XVII) may be made from halides (XVIII) using standard malonate type chemistry.



(V)



(XVIII)

There is further provided by the present invention a general interconversion process (D) wherein compounds of formula (I) can be converted into corresponding compounds of formula (I) by employing suitable reaction techniques. For example, compounds of formula (I) wherein R^3 represents a halogen atom, such as chlorine, may be converted into corresponding compound of formula (I) wherein R^3 represents hydrogen by appropriate reducing reactions. Compounds in which R^3 and/or R^4 represent hydrogen can be converted into compounds in which R^3 and/or R^4 represent a halogen by adding a suitable halogen compound to the compound in the presence of glacial acetic acid.

According to another general process (E), a compound of formula (I) may be prepared by subjecting a protected derivative of a compound of formula (I) to reaction to remove the protecting group or groups.

Thus, at an earlier stage in the preparation of a compound of formula (I) it may have been necessary and/or desirable to protect one or more sensitive groups in the molecule to prevent undesirable side reactions.

The protecting groups used in the preparation of compounds of formula (I) may be used in conventional manner. See for example 'Protective Groups in Organic Chemistry' Ed.J.F.W. McOmie (Plenum Press 1973) or 'Protective Groups in Organic Synthesis' by Theodora W Greene (John Wiley and Sons 1991).

As will be appreciated, in general process (A) described above it may be desirable or even necessary to protect any sensitive groups in the molecule as just described. Thus, a reaction step involving deprotection of a protected derivative of general formula (I) or a salt thereof may be carried out subsequent to the above described process (A).

Compounds of the invention may be isolated in association with solvent molecules by crystallisation from or evaporation of an appropriate solvent.

Individual enantiomers of the compounds of the invention may be prepared from racemates by resolution using methods known in the art for the separation of racemic mixtures into their constituent enantiomers, for example using chiral HPLC.

As well as being employed as the last main step in the preparative sequence, the general methods indicated above for the preparation of the compounds of the invention may also be used for the introduction of the desired

groups at an intermediate stage in the preparation of the required compound. It should therefore be appreciated that in such multi-stage processes, the sequence of reactions should be chosen in order that the reaction conditions do not affect groups present in the molecule which are desired in the final product.

The invention is further illustrated by the following Examples which should not be construed as constituting a limitation thereto.

Intermediate 1

4-Bromomethyl-7-chloro-benzofuran

A mixture of 7-chloro-4-methyl-benzofuran (CAS-number 79444-97-6; 51.9g), N-bromosuccinimide (61.4g), benzoyl peroxide (0.52g) and carbon tetrachloride (1200ml) was heated under reflux under the illumination of an 80W flood lamp for 20h. The mixture was cooled, and filtered and the filtrate evaporated to dryness. The residue was absorbed onto silica and purified by chromatography on silica using ethyl acetate and hexane (1:20) to give the title compound (39.50g) as a yellow solid.

Tlc SiO_2(cyclohexane) Rf 0.30

Intermediate 2

7-Chloro-benzofuran-4-carbaldehyde

A solution of the N-methylmorpholine-N-oxide (37.64g) in acetonitrile (370ml) containing 3Å molecular sieves (36.6g) was stirred at room temperature overnight and cooled in ice. A solution of 4-bromomethyl-7-chloro-benzofuran (39.44g) in acetonitrile (90ml) was added and the mixture stirred in at 0°C for 4h. The mixture was filtered and the filtrate evaporated to dryness. Water and ethyl acetate were added to the residue and the organic phase separated, dried (Na_2SO_4) and evaporated to give the title compound (21.3g) as a pale yellow solid.

Tlc SiO_2(Ethyl acetate/cyclohexane 1:6) Rf 0.40

Intermediate 3

(E)-3-(7-Chloro-benzofuran-4-yl)-acrylonitrile and (Z)-3-(7-Chloro-benzofuran-4-yl)-acrylonitrile

A solution of diethyl cyanomethylphosphonate (7.34g) in dry tetrahydrofuran (20ml) was added to a suspension of sodium hydride (60% oil dispersion; 1.65g) in THF (40ml) over 5 mins with ice cooling. After 15 min, a solution of 7-chloro-benzofuran-4-carbaldehyde in THF (20ml) was added and after 5 mins the solution was warmed up and stirred at room temperature for 2h. Brine (40ml) and ethyl acetate (40ml) were added, the phases separated and the aqueous extracted with ethyl acetate (2x20ml). The extracts were dried ($MgSO_4$) and evaporated and the residue crystallised from ethanol to give off-white fluffy needles (2.95g) of (E)-3-(7-Chloro-benzofuran-4-yl)-acrylonitrile.

Mass Spec Found MNH_4^+ = 221

The mother liquors were evaporated and the residue (6g) chromatographed on silica using ethyl acetate:hexane (1:5 changing to 1:4) to give more of the E-isomer (1.19g) and a sample of the Z-isomer (0.62g).

Mass Spec Found MNH_4^+ = 221

Tlc SiO_2 (Ethyl acetate/hexane 1:5) E-isomer Rf 0.55, Z-isomer Rf 0.35

Intermediate 4

3-(2,3-Dihydro-benzofuran-4-yl)-propylamine hydrochloride

A solution of the (E)-3-(7-chloro-benzofuran-4-yl)-acrylonitrile (intermediate 3) (1.0g) in acetic acid (30ml) containing 10% palladium on charcoal (50mg; 50% wet paste) and 5% platinium on charcoal (50mg) was hydrogenated at 100psi and 50° for 3 days. The solution was filtered through hyflo and evaporated to dryness and the residue recrystallised from isopropanol to give the title compound as white plates (583mg).

Tlc SiO_2 (Dichloromethane/methanol/0.880 ammonia 75:8:1) Rf 0.25

Mass spectrum MH^+ 178

Subjecting the Z-isomer to hydrogenation under similar conditions gave the same product.

Alternative Route

A solution of 2-(2,3-dihydrobenzofuran-4-yl)-propanonitrile (1.20g) in tetrahydrofuran (12ml) was treated with a 1M solution of borane in tetrahydrofuran (12ml) and the solution was heated at reflux for 1h. The solution was cooled to 20° and quenched with methanol (0.5ml) followed by 5M hydrochloric acid (8ml). The solution was heated at reflux for 30min then cooled to 20° and basified with 10M sodium hydroxide (7ml). The mixture was extracted with tert-butyl methyl ether (25ml + 12ml). The combined extracts were dried (K_2CO_3) and the solvent evaporated to give the free base of the title compound (1.43g) as a yellow oil.

Mass spectrum MH^+ 178.

Intermediate 5

3-(5-Bromo-2,3-dihydro-benzofuran-4-yl)-propylamine

A solution of the free base (200mg) liberated from 3-(2,3-dihydro-benzofuran-4-yl)-propylamine hydrochloride and N-bromosuccinimide (215mg) in acetic acid (5ml) was stirred at room temperature overnight. The solution was evaporated to dryness and the residue taken up in water, basified to pH9-10 with 2N sodium hydroxide and extracted with ethyl acetate. The extracts were dried and evaporated to give the title compound (256mg) as a pale yellow oil.

Tlc SiO_2 (Dichloromethane/methanol/0.880 ammonia 75:8:1) Rf 0.53

Mass spectrum found MH^+ 256/258

The hydrochloride salt was prepared by dissolving the title compound in methanolic HCl and evaporating the solvent to give a colourless solid.

Intermediate 6

2-(7-Chloro-benzofuran-4-ylmethyl)-malonic acid diethyl ester

Diethyl malonate (1.7ml) was added dropwise to a suspension of sodium hydride (60%; 0.3g) in dry THF (40ml) at 0° under nitrogen. The mixture was allowed to warm to room temperature over 15 mins. Then a solution of 4-

bromomethyl-7-chloro-benzofuran in dry THF (10ml) was added in one portion and the mixture stirred for 1 h, then partitioned between water (100ml) and ethyl acetate (3x50ml). The combined organic extracts were washed with brine (50ml) ,dried ($MgSO_4$) and evaporated to give the title compound as a pale yellow oil (2.466g)

Tlc SiO_2 (Ether / cyclohexane 1:5) Rf 0.33

Intermediate 7

3-(7-Chloro-benzofuran-4-yl)-acrylic acid methyl ester

Trimethylphosphonoacetate (363mg) in dry DME (1ml) was added dropwise to a suspension of sodium hydride (60%; 329mg) in dry DME (20ml) at 0° under nitrogen. The resulting white precipitate was stirred for 40mins at room temperature, then a solution of 7-chloro-benzofuran-4-carbaldehyde (intermediate 2) (1.238g) in dry DME (15ml) was added at room temperature over 1 min. The mixture was heated under reflux for 2h, cooled to room temperature, then partitioned between water (150ml) and ether (100ml). The combined organic extracts were washed with brine (100ml) and dried ($MgSO_4$). The solvent was evaporated to give the title compound as a colourless solid (1.59g)

Tlc SiO_2 (Dichloromethane / cyclohexane 1:1) Rf 0.35

Intermediate 8

3-(7-Chloro-benzofuran-4-yl)-propionic acid ethyl ester

A mixture of 2-(7-chloro-benzofuran-4-ylmethyl)-malonic acid diethyl ester (2.47g) and sodium chloride (0.656g) in DMSO (12ml) and water (0.5ml) was heated at 200° for 4h under nitrogen. The cooled mixture was partitioned between water (80ml) and ether (3x50ml) and the combined organic extracts washed with brine (3x50ml) and dried ($MgSO_4$). The solvent was evaporated to give the title compound as a brown oil (1.28g)

Tlc SiO_2 (Ether / cyclohexane 1:5) Rf 0.4

Intermediate 9

3-(7-Chloro-benzofuran-4-yl)-propan-1-ol

Route A

Lithium aluminium hydride (1.0M in ether; 0.24ml) was added dropwise to a solution of 3-(7-chloro-benzofuran-4-yl)-acrylic acid methyl ester (intermediate 7) (0.1g) in dry THF(5ml) at 0° under nitrogen. The mixture was stirred at 0° for 5mins, then water (0.2ml) in THF (2ml) added dropwise. The solvent was evaporated and the residue partitioned between hydrochloric acid (2N; 10ml) and ether (3x20ml). The combined organic extracts were washed with brine (20ml) and dried ($MgSO_4$). The solvent was evaporated and the residue purified by column chromatography, eluting with ether / cyclohexane 2:1 gave the title compound as a colourless gum (29mg)

Tlc SiO_2 (Ether / cyclohexane 2:1) Rf 0.25

Route B

Lithium aluminium hydride (1.0M in ether; 2.5ml) was added dropwise to a solution of 3-(7-chloro-benzofuran-4-yl)-propionic acid ethyl ester (intermediate 8) (0.588g) in dry THF(intermediate 8) (5ml) at 0° under nitrogen. The mixture was allowed to warm to room temperature and stirred for 0.5h, cooled to 0° and water (1ml) in THF (5ml) added dropwise. Hydrochloric acid (2N; 2ml) was added followed by water (10ml) and the mixture extracted with ethyl acetate (3x20ml). The combined organic extracts were washed with brine (20ml) and dried ($MgSO_4$). The solvent was evaporated and the residue purified by column chromatography, eluting with ether / cyclohexane 3:2 gave the title compound as a colourless gum (360mg)

Tlc SiO_2 (Ether / cyclohexane 2:1) Rf 0.25

Intermediate 10

2-[3-(7-Chloro-benzofuran-4-yl)-propyl]-isoindole-1,3-dione

Diethylazodicarboxylate (0.35ml) was added dropwise to a solution of triphenylphosphine (587mg) and phthalimide (329mg) in dry THF (10ml) at 0° under nitrogen. A solution of 3-(7-chloro-benzofuran-4-yl)-propan-1-ol (364mg) in THF (5ml) was then added and the mixture allowed to warm to room temperature and stirred for 2h. The solvent was evaporated and the residue purified by column chromatography, eluting with cyclohexane / ether 3:1 gave the title compound as a colourless solid (521mg)

Tlc SiO_2 (Cyclohexane / ether 3:1) Rf 0.24

Intermediate 11

1-Chloro-4-(2,2-diethoxy-ethoxy)-2-methyl-benzene

A mixture of 4-chloro-3-methylphenol (47g), bromoacetaldehyde diethyl acetal (45ml) and potassium hydroxide (33.6g) in dimethyl sulphoxide (250ml) was heated at 120° for 2h. The cooled mixture was partitioned between water (750ml) and toluene (3x 500ml) and the combined organic extracts washed with brine / water 1:1 (3x300ml) and dried (Na_2SO_4). The solvent was evaporated to give the title compound as a pale yellow oil (67.9g)

Tlc SiO_2 (Hexane) Rf 0.2

Intermediate 12

5-Chloro-4-methyl-benzofuran mixture with 5-chloro-6-methyl-benzofuran

A solution of 1-chloro-4-(2,2-diethoxy-ethoxy)-2-methyl-benzene (36.2g) in toluene (150ml) was added dropwise to a solution of polyphosphoric acid (72g) in toluene (200ml) at 100° under nitrogen. The mixture was heated at 100° for 1h, cooled to room temperature and sodium hydroxide (2M,400ml) was added. The organic phase was separated and the aqueous extracted further with toluene (2x200ml). The combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography. Elution with cyclohexane gave the title compound as a pale yellow oil (20.1g)

Tlc SiO_2 (Cyclohexane) Rf 0.54

Intermediate 13

4-Bromomethyl-5-chloro-benzofuran mixture with 6-bromomethyl-5-chloro-benzofuran

A mixture of 5-chloro-4-methyl-benzofuran with 5-chloro-6-methyl-benzofuran (19.6g), N-bromosuccinimide (23g) and benzoyl peroxide (160mg) in carbon tetrachloride (350ml) was heated under reflux under a 200W lamp for 36h. The cooled mixture was filtered through hyflo and the filtrate evaporated to give the title compound as a dark oil (28.8g)

Tlc SiO_2 (Cyclohexane) Rf 0.6

Intermediate 14

5-Chloro-benzofuran-4-carbaldehyde mixture with 5-chloro-benzofuran-6-carbaldehyde

A solution of 4-bromomethyl-5-chloro-benzofuran mixture with 6-bromomethyl-5-chloro-benzofuran (30.54g) in dry acetonitrile (80ml) was added dropwise to a mixture of N-methylmorpholine-N-oxide (29.14g) and 4Å molecular sieves in dry acetonitrile (100ml) at 10° under nitrogen. The mixture was stirred at room temperature for 5h, filtered through hyflo and the filtrate evaporated. The residue was triturated under ether (100ml) and filtered. The filtrate was evaporated and the residue recrystalised from cyclohexane to give the title compound as a pale yellow solid (10.95g)

Tlc SiO_2 (Dichloromethane/Hexane 1:1) Rf 0.3

Intermediate 15

(E)-3-(5-Chloro-benzofuran-4-yl)-acrylonitrile mixture with (E)-3-(5-Chloro-benzofuran-6-yl)-acrylonitrile

A solution of diethyl cyanomethylphosphonate (11.5ml) in dry ethylene glycol dimethyl ether (DME; 10ml) was added dropwise to a suspension of sodium hydride (60%; 2.914g) in DME (50ml) at 0° under nitrogen. The mixture was stirred at 0° for 20 mins. Then a solution of 5-chloro-benzofuran-4-carbaldehyde mixture with 5-chloro-benzofuran-6-carbaldehyde (10.95g) in DME (50ml) was added in one portion. The mixture was heated at 60° for 2h, cooled to room temperature and partitioned betweem water (150ml) and ether (3x100ml). The combined organic extracts were washed with brine (2x100ml) and dried ($MgSO_4$). The solvent was evaporated and the residue purified by column chromatography. Elution with cyclohexane / ethyl acetate 20:1 gave the title compound as a colourless solid (6.75g)

Tlc SiO_2 (Cyclohexane / ethyl acetate 8:1) Rf 0.31

Intermediate 16

3-(5-Chloro-benzofuran-4-yl)-propylamine mixture with 3-(5-chloro-benzofuran-6-yl)-propylamine

A solution of (E)-3-(5-chloro-benzofuran-4-yl)-acrylonitrile mixture with (E)-3-(5-chloro-benzofuran-6-yl)-acrylonitrile (intermediate 15) (1g) in ethanolic ammonia (1.0M, 50ml) was hydrogenated over rhodium on alumina (130mg) for 18h. The catalyst was filtered off and the filtrate evaporated. The residue was purified by column chromatography , eluting with dichloromethane / ethanol / ammonia 100:8:1 gave the title compound as a pale yellow gum (616mg)

Tlc SiO_2 (Dichloromethane / ethanol / ammonia 100:8:1) Rf 0.15

Intermediate 17

2-(2,2-Dimethoxy-ethoxy)-1-fluoro-4-methyl-benzene

Bromoacetaldehyde dimethyl acetal (42ml) was added to a mixture of 2-fluoro 5-methyl phenol[1] (22.05g) and potassium hydroxide pellets (19.6g) in dimethyl sulphoxide (160ml) at room temp. under nitrogen. The mixture was heated at 100° for 16h, cooled to room temp. and partitioned between water (500ml) and ether (3x200ml). The combined organic extracts were washed with brine/water

1:1, (3x200ml) and dried ($MgSO_4$). The solvent was evaporated to give the title compound as an orange oil (48g)

Tlc (Cyclohexane) Rf 0.4

Reference 1: Singh S et al, J Amer. Chem Soc 1987, 109, (23), 7194-7196.

Intermediate 18

7-Fluoro-4-methyl-benzofuran

A solution of 2-(2,2-dimethoxy-ethoxy)-1-fluoro-4-methyl-benzene (48g) in toluene (50ml) was added dropwise to a refluxing solution of polyphosphoric acid (100g) in toluene (350ml) under nitrogen. The mixture was heated under reflux for 3h, cooled to room temperature and sodium hydroxide (2N; 800ml) added. The mixture was extracted with ether (3x300ml) and the combined organic extracts washed with brine (2x300ml) and dried ($MgSO_4$). The solvent was evaporated and the residue purified by column chromatography. Eluting with hexane gave the title compound as a pale yellow oil (14.2g)

Tlc SiO_2 (Hexane) Rf 0.4

Intermediate 19

4-Bromomethyl-7-fluoro-benzofuran

A mixture of 7-fluoro-4-methyl-benzofuran (14.2g), N-bromosuccinimide (19.7g), benzoyl peroxide (0.5g) and carbon tetrachloride (600ml) was heated under reflux under the illumination of an 80W flood lamp for 20h. The mixture was cooled, and filtered and the filtrate evaporated to dryness to give the title compound as a pale orange oil (23.4g)

Tlc (cyclohexane) Rf 0.18

Intermediate 20

7-Fluoro-benzofuran-4-carbaldehyde

A solution of the N-methylmorpholine-N-oxide (22.24) in acetonitrile (250ml) containing 3Å molecular sieves (8.71g) was stirred at room temperature overnight, then cooled in ice. A solution of 4-bromomethyl-7-fluoro-benzofuran (23.45g) in acetonitrile (50ml) was added and the mixture stirred for 4h. The mixture was filtered and the filtrate evaporated to dryness. Water and ether were added to the residue and the organic phase separated, washed with brine (2x200ml), dried ($MgSO_4$) and evaporated . The residue was triturated under ether (50ml) and filtered to give the title compound as a pale yellow solid (5.45g)

Tlc SiO_2 (Dichloromethane / hexane 1:1) Rf 0.30

Intermediate 21

(E)-3-(7-Fluoro-benzofuran-4-yl)-acrylonitrile

A solution of diethyl cyanomethylphosphonate (5.35g) in dry ethylene glycol dimethyl ether (DME; 20ml) was added to a suspension of sodium hydride (60% oil dispersion; 1.32g) in DME (20ml) at 0° under nitrogen over 5 mins. After 15 min, a solution 7-fluoro-benzofuran-4-carbaldehyde (4.51g) in DME (20ml) was added and after 5 mins the solution was warmed up and stirred at room temperature for 2h. Ammonium chloride solution (200ml) and ethyl acetate (150ml) were added, the phases separated and the aqueous extracted with ethyl acetate (2x150ml). The extracts were dried ($MgSO_4$) and evaporated and the residue triturated under ether (20ml) and filtered to give the E isomer as a buff coloured solid (3.07g)

The mother liquors were evaporated to give a mixture of E and Z isomers (4.25g)

Tlc SiO_2 (Hexane / Dichloromethane 1:1) Rf 0.40

Intermediate 22

3-(7-Fluoro-2,3-dihydro-benzofuran-4-yl)-propylamine

A solution of (E)-3-(7-fluoro-benzofuran-4-yl)-acrylonitrile (0.25g) in ethanol (25ml), ammonia (0.88; 10ml) containing 10% palladium on charcoal (50mg; 50% wet paste) and 5% rhodium on charcoal (50mg) was hydrogenated at 70psi and 70° for 18h. The solution was filtered through hyflo and evaporated to dryness and the residue purified by column chromatography. Eluting with dichloromethane / ethanol / ammonia 100:8:1 gave the title compound (256mg).

Tlc (Dichloromethane/methanol/0.880 ammonia 100:8:1) Rf 0.20
Mass spectrum Found MH^+ 196

Intermediate 23

3-(5-chloro-2,3-dihydro-benzofuran-4-yl) propylamine hydrochloride

A solution of of 3-(2,3-dihydro-benzofuran-4-yl)-propylamine hydrochloride (150mg) and N-chlorosuccinimide (100mg) in acetic acid (50ml) was stirred at room temperature overnight. The solution was evaporated to dryness and the residue taken up in water, basified with 2N sodium hydroxide and extracted with dichloromethane. The extracts were dried and evaporated and the residue disolved in a solution of hydrogen chloride in methanol. Evaporation gave the the title compound (159mg) as an off-white powder after trituration with ether.

Mass spectrum Found MH^+ 212/214.

Intermediate 24

Cyclopropanecarboxylic acid [3-(3-hydroxy-phenyl)-propyl]-amide

Cyclopropanecarbonyl chloride (0.063ml) was added dropwise to a suspension of 3-(3-amino-propyl)-phenol[1] (0.1g) and N,N-diisopropylamine (0.23ml) in dichloromethane (15ml) in an ice bath under nitrogen. The mixture was then stirred for 3h at room temperature, then purified by passing through a solid phase extraction cartridge. Elution with chloroform followed by ethyl acetate gave the title compound as a colourless gum (122mg)

TLC SiO_2 (Ether) Rf 0.34

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Intermediate 25

Cyclopropanecarboxylic acid [3-(3-prop-2-ynyloxy-phenyl)-propyl]-amide

Propargyl bromide (80% in toluene, 0.091ml) was added dropwise to a mixture of cyclopropanecarboxylic acid [3-(3-hydroxy-phenyl)-propyl]-amide (122mg) and potassium carbonate (154mg) in dry DMF (10ml) in an ice bath under nitrogen. The mixture was allowed to warm to room temperature, then heated at 65°C for 18h. The cooled mixture was partitioned between water (50ml) and ethyl acetate (3x15ml). The combined organic extracts were washed with brine / water 1:1 (3x20ml) and dried ($MgSO_4$). The solvent was evaporated and the residue purified by column chromatography on silica. Elution with hexane / ethyl acetate 2:1 gave the title compound as a colourless solid (79mg)

Tlc SiO_2 (Hexane / ethyl acetate 2:1) Rf 0.18

Intermediate 26

1-(2,2-Dimethoxyethoxy)-4-fluoro-3-methylbenzene

A mixture of 4-fluoro-3-methylphenol (36.7g), potassium hydroxide pellets (19.5g) and bromoacetaldehyde dimethyl acetal (34.6ml) in dimethyl sulphoxide (240ml) was heated at 110° for 24h. The mixture was cooled, diluted with water (350ml) and extracted with hexane. Evaporation of the extracts gave the title compound as an oil (52.3g).

Mass spec. Found MNH_4^+ 232

Intermediate 27

5-Fluoro-4-methylbenzofuran mixture with 5-Fluoro-6-methylbenzofuran

Polyphosphoric acid (185g) was heated to 100° and a solution of 1-(2,2-dimethoxyethoxy)-4-fluoro-3-methylbenzene (52.3g) in toluene (520ml) added. The mixture was stirred under reflux for 5h, cooled and the toluene decanted off. The solution was concentrated and the residue passed through silica (900g)

eluting with hexane. Evaporation gave the title compound as a colourless liquid (14.95g).

Tlc (hexane) Rf 0.60

Intermediate 28

4-Bromomethyl-5-fluorobenzofuran mixture with 6-Bromomethyl-5-fluorobenzofuran

A mixture of 5-fluoro-4-methylbenzofuran and 5-fluoro-6-methylbenzofuran (14.95g), N-bromosuccinimide (16.57g), benzoyl peroxide (0.32g) and carbon tetrachloride (375ml) was heated under reflux under the illumination of an 80W flood lamp for 20h. The mixture was cooled, and filtered and the filtrate evaporated to dryness to give the crude product as an oil (24.0g). This material was combined with a similar crude product (6.94g) from an identical reaction run on a smaller scale and purified by chromatography on silica (900g) using an ether hexane mixture (1:30) as eluant to give the title compound (13.5g) as an oil.

Tlc (hexane) Rf 0.38

Intermediate 29

5-Fluorobenzofuran-4-carbaldehyde (A) mixture with 5-Fluorobenzofuran-6-carbaldehyde (B)

A solution of the N-methylmorpholine-N-oxide (13.6g) in acetonitrile (135ml) containing 3Å molecular sieves (13.2g) was stirred at room temperature overnight and cooled in ice. A solution of 4-bromomethyl-5-fluorobenzofuran and 6-bromomethyl-5-fluorobenzofuran (13.33g) in acetonitrile (35ml) was added and the mixture stirred at 5° for 4h. The mixture was filtered and the filtrate evaporated to dryness. Water and ethyl acetate were added to the residue and the organic phase separated, dried and evaporated to give the mixture of aldehydes. The mixture was separated by chromatography on silica (600g) using a mixture of ethyl acetate and hexane (1:9) as the eluant to give the title compound (A) (2.19g);

Tlc (Ethyl acetate/hexane 1:9) Rf 0.47

Mass spec. Found MNH_4^+ 182

and the title compound (B) (2.17g)

Tlc (Ethyl acetate/hexane 1:9) Rf 0.35

Mass spec. Found MNH_4^+ 182

Intermediate 30

(E)- 3-[5-Fluororobenzofuran-4-yl]acrylonitrile and (Z)-3-[5-Fluorobenzofuran-4-yl] acrylonitrile.

A solution of diethyl cyanophosphonate (2.79g) in dry tetrahydrofuran (10ml) was added to a suspension of sodium hydride (60% oil dispersion; 0.63g) in THF (16ml) over 5 mins with ice cooling. After 15 min, a solution of 5-fluorobenzofuran-4-carbaldehyde (2.15g) in THF (10ml) was added and after 5 mins the solution was warmed up and stirred at room temperature for 3h. Brine (20ml) and ethyl acetate (20ml) were added, the phases separated and the aqueous extracted with ethyl acetate (2x25ml). The extracts were dried and evaporated and the residue purified by chromatography (Biotage Flash 40; 90g; ethyl acetate:hexane 1:9) to give the title compound as a cream solid (1.97g)

Tlc (Ethyl acetate/hexane 1:9) Rf 0.25
Mass spectrum MNH_4^+ 205

Intermediate 31

3-(2,3-Dihydro-5-fluorobenzofuran-4-yl)propylamine hydrochloride

N-[3-[2,3-Dihydro-5-fluorobenzofuran-4-yl]propyl]acetamide (0.55g) was heated under reflux in 2M hydrochloric acid (10ml) for 24h. The mixture was cooled and washed with dichloromethane, basified with 2M sodium hydroxide and extracted with dichloromethane. Evaporation of the extracts gave an oil which was

dissolved in 0.7M methanolic hydrogen chloride (8ml). Evaporation gave the title compound as a beige solid (0.28g).

Mass spectrum MH^+ 196

Intermediate 32

2,3-Bis(2-hydroxyethyl)-phenol

A solution of 5,8-dihydronaphth-1-ol (2.00g) in methanol (40ml) was cooled to -70° and ozone in oxygen was bubbled through the solution until tlc indicated that all the starting material had been consumed. The ozone was switched off and nitrogen bubbled through the solution for 5min. Sodium borohydride (454mg) was then added and the solution allowed to warm slowly to 20°. A further portion of sodium borohydride (227mg) was added, followed 10min later by acetic acid (1ml) and then the solvent was evaporated. The residue was partitioned between 2M hydrochloric acid (50ml) and ethyl acetate (2x50ml). The combined ethyl acetate extracts were dried (Na_2SO_4) and the solvent evaporated to give a brown oil which was purified by chromatography on silica gel eluting with ethyl acetate to give the title compound (1.49g) as a pale brown oil which crystallised on prolonged standing.

Tlc SiO_2 (ethyl acetate) Rf 0.46.

Intermediate 33

2-(2,3-Dihydrobenzofuran-4-yl)-ethanol

A mixture of 2,3-bis(2-hydroxyethyl)-phenol (1.2g) and 36% aqueous hydrochloric acid (24ml) was heated at reflux for 2h. The mixture was cooled, diluted with water (24ml) and extracted with ethyl acetate (2x24ml). The combined extracts were dried (Na_2SO_4) and the solvent evaporated to give the title compound (1.2g) as a brown oil.

Tlc SiO_2 (ethyl acetate) Rf 0.67.

Intermediate 34

Methanesulfonic acid 2-(2,3-dihydrobenzofuran-4-yl)-ethyl ester

A solution of 2-(2,3-dihydrobenzofuran-4-yl)-ethanol (1.13g) in dichloromethane (11ml) was treated with triethylamine (1.25ml), followed by methanesulfonyl chloride (0.64ml). After 5min the reaction mixture was poured into 2M hydrochloric acid (10ml) and extracted with dichloromethane (2x10ml). The combined extracts were washed with water (10ml), dried (Na_2SO_4) and the solvent evaporated to give the title compound (1.76g) as a yellow oil.

Tlc SiO_2 (iso-hexane/ethyl acetate 1:1) Rf 0.43.

Intermediate 35

3-(2,3-Dihydrobenzofuran-4-yl)-propanonitrile

A solution of methanesulfonic acid 2-(2,3-dihydrobenzofuran-4-yl)-ethyl ester (1.71g) in dimethylsulfoxide (14ml) was treated with sodium cyanide (381mg) and heated at 80° for 1h. The suspension was cooled to 20°, diluted with water (14ml) and extracted with ethyl acetate (2x17ml). The combined extracts were washed with 5% aqueous sodium chloride (17ml), dried (Na_2SO_4) and the solvent evaporated to give the title compound (1.22g) as a brown oil which crystallised on standing.

Tlc SiO_2 (iso-hexane/ethyl acetate 1:1) Rf 0.62.

Example 1

N-[3-(5-Bromo-2,3-dihydro-benzofuran-4-yl)-propyl]-acetamide

A solution of 3-(5-bromo-2,3-dihydro-benzofuran-4-yl)-propylamine (256mg) in pyridine (3ml) at 4° was treated with acetic anhydride (0.11ml) and the solution stored overnight at 4°. The cold solution was acidified with 2N hydrochloric acid and the mixture extracted with ethyl acetate. The extracts were dried and evaporated and the residue chromatographed on silica (20g) using dichloromethane:methanol:ammonia (100:8:1) to give the title compound as an oil which slowly solidified (175mg).

Tlc SiO_2 (Dichloromethane/methanol/0.880 ammonia 75:8:1) Rf 0.67
Mass spectrum MH^+ Found 297/299

Example 2

N-[3-(7-Chloro-benzofuran-4-yl)-propyl]-acetamide

A solution of 2-[3-(7-chloro-benzofuran-4-yl)-propyl]-isoindole-1,3-dione (0.5g) in ethanolic methylamine (10ml) was stirred at room temperature for 4h. The solvent was evaporated and the residue suspended in dry THF (15ml) and cooled to 0° C. Pyridine (0.27ml) and acetic anhydride (0.2ml) were added and the mixture allowed to warm to room temperature and stirred for 18h. The solvent was evaporated and the residue purified by column chromatography, eluting with dichloromethane / methanol 100:1 gave the title compound as a colourless solid (230mg) mp 61-62°

Tlc SiO_2 (Dichloromethane / methanol 50:1) Rf 0.16

A solution of E- and Z-3-[7-chlorobenzofuran-4-yl]acrylonitrile (4.0g) in acetic acid (100ml) and acetic anhydride (3.7ml) containing 10% palladium on charcoal (200mg; 50% wet paste) and 5% platinium on charcoal (200mg) was hydrogenated at 100psi and 60° for 24h. An aliquot (10ml) was removed and methanol (1ml) added to it. After 16h the solution was filtered and evaporated and the residue purified by chromatography (Biotage Flash 40; ethyl acetate) to give the title amide (99mg) as an oil.

Tlc (Ethyl acetate) Rf 0.30
Mass spectrum MH^+ 252/254

Example 3

N-[3-(7-Chloro-2,3-dihydro-benzofuran-4-yl)-propyl]-acetamide

A solution of N-[3-(7-chloro-benzofuran-4-yl)-propyl]-acetamide (48mg) in ethanol (15ml) was hydrogenated over rhodium catalyst (5% on carbon; 15mg) over 7h. The catalyst was filtered off and the filtrate evaporated. The residue was purified by column chromatography, eluting with dichloromethane /

methanol 50:1 gave the title compound as a colourless solid (37.6mg) mp 76-78°

Mass Spec Found MH^+ 254/256

Tlc SiO_2 (Dichloromethane / methanol 50:1) Rf 0.16

Example 4

N-[3-(2,3-Dihydro-benzofuran-4-yl)-propyl]-acetamide

A solution of the N-[3-(7-chloro-2,3-dihydro-benzofuran-4-yl)-propyl]-acetamide, (78mg) in ethanol (5ml) was hydrogenated over palladium (10%; 20mg) over 64h. The catalyst was filtered off and the filtrate concentrated in vacuo. The residue was purified by column chromatography , eluting with dichloromethane / methanol 50:1 gave the title compound as a colourless solid (54mg) mp 66-67°C

Assay Found : C, 71.0 ; H, 8.1 ; N, 6.6 ;
$C_{13}H_{17}NO_2$ Requires: C, 71.2 ; H, 7.8 ; N, 6.4%

Tlc SiO_2 (Dichloromethane / Methanol 50:1) Rf 0.16

Alternative Route

A solution of E- and Z-3-[7-chlorobenzofuran-4-yl]acrylonitrile (15g) in acetic acid (330ml), acetic anhydride (19.6ml) and triethylamine (30.75ml) containing 10% palladium on charcoal (0.75g; 50% wet paste) and 5% platinium on charcoal (0.75g) was hydrogenated at 150psi and 75° for 4 days. More catalysts (as before) were added and the reaction continued for a further 24h. The solution was filtered and evaporated and the residue partitioned between dichloromethane (250ml) and water (150ml). The organic layer was washed successively with water (150ml), 2M hydrochloric acid (2x100ml), water (100ml) and 2M sodium carbonate (100ml) and then dried and evaporated to give the title compound as an off-white solid (15.4g).

Tlc (Dichloromethane/methanol 50:1) Rf 0.16
Mass spectrum MH^+ 220

Example 5

N-[3-(5-Chloro-benzofuran-4-yl)-propyl]-acetamide

Acetic anhydride (1.95ml) was added dropwise to a solution of 3-(5-chloro-benzofuran-4-yl)-propylamine mixture with 3-(5-chloro-benzofuran-6-yl)-propylamine (2.86g) and pyridine (2.2ml) in dry THF (70ml) at 0° under nitrogen. The mixture was stirred at room temperature for 3h, then evaporated to dryness in vacuo . The residue was purified by HPLC (CN-PK5-10530 column). Eluting with 5% isopropanol / heptane gave the title compound as a colourless solid (1.37g) mp 82-83 °C.

Tlc SiO_2 (Dichloromethane / ethanol / 0.880 ammonia 100:8:1) Rf 0.39

Example 6

N-[3-(5-Chloro-2,3-dihydro-benzofuran-4-yl)-propyl]-acetamide

A solution of N-[3-(5-chloro-benzofuran-4-yl)-propyl]-acetamide (0.25g) in ethanol (15ml) was hydrogenated over 5% rhodium on carbon (80mg) for 18h. The catalyst was filtered off and the filtrate evaporated. The residue was purified by column chromatography on silica, eluting with dichloromethane / methanol 40:1 gave the title compound as a colourless solid (131mg) mp 91-92

Mass Spec Found MH^+ = 254.094828
$C_{13}H_{17}ClNO_2$ Requires 254.094782

Tlc SiO_2 (Dichloromethane / Methanol 50:1) Rf 0.22

Example 7

N-[3-(5,7-Dichloro-2,3-dihydro-benzofuran-4-yl)-propyl]-acetamide

N-Chlorosuccinimide (173mg) was added to a solution of N-[3-(5-chloro-2,3-dihydro-benzofuran-4-yl)-propyl]-acetamide (0.2g) in glacial acetic acid (5ml) at

room temperature under nitrogen and the mixture stirred for 64h. The solution was adusted to pH 9 with sodium carbonate (2N; 10ml) and extracted with ethyl acetate (3x15ml). The combined organic extracts were washed with brine (20ml) and dried ($MgSO_4$). The solvent was evaporated and the residue purified by HPLC, eluting with 50% acetonitrile / water + 0.1% TFA gave the title compound as a colourless gum (97mg)

Mass Spec Found MH^+ = 288.055872
$C_{13}H_{16}Cl_2NO_2$ requires 288.055809

Tlc SiO_2 (Dichloromethane / Methanol 50:1) Rf 0.22

Example 8

N-[3-(7-Fluoro-2,3-dihydro-benzofuran-4-yl)-propyl]-acetamide
Acetic anhydride (0.18ml) was added dropwise to a solution of 3-(7-fluoro-2,3-dihydro-benzofuran-4-yl)-propylamine (256mg) in dry THF (10ml) containing pyridine (0.21ml) at 0° under nitrogen and the solution stirred overnight at room temperature. The solution was evaporated and the residue purified by column chromatography . Eluting with dichloromethane:methanol: (50:1) gave the title compound as a colourless oil (133mg)

Tlc (Dichloromethane/methanol 50:1) Rf 0.18
Mass Spectrum Found MH^+ 238 , MNH_4^+ 255

Example 9

N-[3-(5-Chloro-7-fluoro-2,3-dihydro-benzofuran-4-yl)-propyl]-acetamide
N-Chlorosuccinimide (47.7mg) was added to a solution of N-[3-(7-fluoro-2,3-dihydro-benzofuran-4-yl)-propyl]-acetamide (77mg) in glacial acetic acid (5ml) at room temperature under nitrogen and the mixture stirred for 72h. The solution was evaporated and the residue partitioned between sodium carbonate (2N; 10ml) and ethyl acetate (10ml). The combined organic extracts were washed with brine (10ml) and dried ($MgSO_4$). The solvent was evaporated and the residue purified by column chromatography. Eluting with dichloromethane /

methanol 50:1 gave the title compound as a colourless gum which crystallised on standing (67mg).

Mass Spec Found MH^+ = 272/274

Tlc SiO_2 (Dichloromethane / Methanol 50:1) Rf 0.18

Example 10

N-[3-(5-Bromo-7-fluoro-2,3-dihydro-benzofuran-4-yl)-propyl]-acetamide

N-Bromosuccinimide (569mg) was added to a solution of N-[3-(7-fluoro-2,3-dihydro-benzofuran-4-yl)-propyl]-acetamide (690mg) in glacial acetic acid (15ml) at room temperature under nitrogen and the mixture stirred for 48h. The solution was evaporated and the residue partitioned between sodium carbonate (2N; 20ml) and ethyl acetate (20ml). The combined organic extracts were washed with brine (25ml) and dried ($MgSO_4$). The solvent was evaporated and the residue purified by column chromatography. Eluting with dichloromethane / methanol 50:1 gave the title compound as a colourlss solid (644mg)

Mass Spec Found MH^+ = 316/318

Tlc SiO_2 (Dichloromethane / Methanol 50:1) Rf 0.18

Example 11

Cyclopropanecarboxylic acid [3-(2,3-dihydro-benzofuran-4-yl)-propyl]-amide

3-(2,3-dihydro-benzofuran-4-yl)-propylamine hydrochloride (200mg) was partitioned between 2N sodium hydroxide (10ml) and dichloromethane (10ml) and the organic phase separated, dried (Na_2SO_4) and evaporated. The residual free base (160mg) and triethylamine (110mg) were dissolved in dichloromethane (2ml), cooled in ice and cyclopropane carbonyl chloride (103mg) added. After 2 hours the solution was warmed up to room temperature and 2N hydrochloric acid (10ml) added. The mixutre was extracted with dichloromethane (3x20ml), and the extracts washed with 8% sodium

bicarbonate, dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silica using a mixture of ethyl acetate and hexane (1:1) as the eluant to give the title compound as a white solid (95mg)

Mass Spec Found MH^+ 246

Tic SiO2 (Ethyl acetate/hexane 1:1) Rf 0.26

Example 12

Cyclopropane carboxylic acid [3-(5-chloro-2,3-dihydro-benzofuran-4-yl)propyl]-amide

A mixture of 3-(5-chloro-2,3-dihydro-benzofuran-4-yl)-propylamine hydrochloride (142mg), dimethylformamide (5 drops), triethylamine (0.64ml) and dichloromethane (5ml) was stirred in ice for 20 minutes. Cyclopropanecarbonyl chloride (66mg) was added and stirring continued for 5 hours. The mixture was purified by chromatography on silica eluting with ethyl acetate/hexane (1:1) to give the title compound as a white solid (80mg).

Tlc (Ethyl acetate / Hexane 1:1) Rf 0.17

Mass spectrum Found MH+ 280/282

Example 13

Cyclopropanecarboxylic acid [3-(5-bromo-2,3-dihydro-benzofuran-4-yl)propyl]-amide

A mixture of 3-(5-bromo-2,3-dihydro-benzofuran-4-yl)-propylamine hydrochloride (100mg), dimethylformamide (3 drops), triethylamine (0.35ml) and dichloromethane (3ml) was stirred in ice for 15 minutes. Cyclopropanecarbonyl chloride (36mg) was added and stirring continued for 2 hours. The mixture was purified by chromatography on silica to give the title compound as a white solid (86mg).

Tlc (Ethyl acetate:hexane 1:1) Rf 0.33

Mass spectrum Found MH+ 324/326

Example 14

Cyclopropanecarboxylic acid [3-(7-fluoro-2,3-dihydro-benzofuran-4-yl)propyl] amide

A mixture of 3-(7-fluoro-2,3-dihydro-benzofuran-4-yl)-propylamine (114mg), triethylamine (0.089ml), dichloromethane (5ml) and cyclopropanecarbonyl chloride (67mg) was stirred in ice for 20 minutes and stirring continued at room temperature overnight. The mixture was partitioned between 2N hydrochloric acid and dichloromethane and the organic phase washed with 8% sodium bicarbonate and evaporated. Purification of the residue by preparative hplc gave the title compound as a white solid (16mg).

Tlc (Ethyl acetate / Hexane 1:1) Rf 0.12

Mass spectrum Found MH+ 264

Example 15

Cyclopropanecarboxylic acid [3-(5-chloro-7-fluoro-2,3-dihydro-benzofuran-4-yl)-propyl]-amide

A mixture of cyclopropanecarboxylic acid [3-(7-fluoro-2,3-dihydro-benzofuran-4-yl)-propyl]-amide (445mg) and N- chlorosuccinimide (248mg) in glacial acetic acid (15ml) was stirred at room temperature for 72h. The solvent was evaporated and the residual solid triturated under water (10ml) and filtered to give the title compound as a colourless solid (236mg).

Mass spec. Found MH^+ 298.1 / 300.1

Tlc SiO_2 (Hexane / ethyl acetate 1:1) Rf0.18

Example 16

Cyclopropanecarboxylic acid [3-(5-chloro-7-fluoro-benzofuran-4-yl)-propyl]-amide

Lead tetraacetate (313mg) was added to a solution of cyclopropanecarboxylic acid [3-(5-chloro-7-fluoro-2,3-dihydro-benzofuran-4-yl)-propyl]-amide (0.2g) in glacial acetic acid (5ml) and the mixture stirred at room temperature for 18h. The solvent was evaporated and the resdue purified by preparitive HPLC to give the title compound as a colourless solid (20mg).

Mass spec Found MH^+ 296.1 / 298.1

Tlc SiO_2 (Hexane / ethyl acetate 1:1) Rf 0.18

Example 17

N-[3-(benzofuran-4-yl)-propyl]-acetamide

Lead tetraacetate (210mg) was added to a solution of N-[3-(2,3-dihydro-benzofuran-4-yl)-propyl]-acetamide (100mg) in acetic acid (1.5ml) at 10°. The mixture was stirred at room temperature for 2h and at 50° for 16h. The solvent was evaporated and the residue purified by chromatography to give the title compound as an oil (41mg).

Mass spec Found MH^+ 218

Tlc SiO_2 (ethyl acetate / hexane 2:1) Rf 0.43

Example 18

Cyclopropanecarboxylic acid [3-(benzofuran-4-yl)-propyl]-amide

Lead tetraacetate (194mg) was added to a solution of cyclopropanecarboxylic acid [3-(2,3-dihydro-benzofuran-4-yl)-propyl]-amide (100mg) in acetic acid (1.5ml) at 10°. The mixture was stirred at room temperature for 4h and at 50° for 24h. The solvent was evaporated and the residue purified by chromatography on silica. Elution with hexane / ethyl acetate gave the title compound as an oil (15mg).

Mass spec Found MH^+ 244

Tlc SiO_2 (Ethyl acetate / hexane 1:1) Rf 0.13

Example 19

Cyclobutanecarboxylic acid [3-(2,3-dihydro-benzofuran-4-yl)-propyl]-amide

3-(2,3-Dihydro-benzofuran-4-yl)-propylamine hydrochloride (100mg) was suspended in dichloromethane (3ml) containing triethylamine (0.33ml) and cooled in ice. A solution of cyclobutanecarbonyl chloride (0.054ml) in dichloromethane (1ml) was added and the mixture stirred in ice for 3h. The mixture was purified by elution through a solid phase extraction cartridge to give the title compound as a white solid (110mg).
Tlc SiO_2 (Ethyl acetate / hexane 1:1) Rf 0.33
Mass spectrum MH^+ 260

Example 20

Cyclopentanecarboxylic acid [3-(2,3-dihydro-benzofuran-4-yl)-propyl]-amide

The compound was prepared by the method described in Example 19 using cyclopentanecarbonyl chloride (0.058ml) to give the title compound as a white solid (90mg).
Tlc SiO_2 (Ethyl acetate / hexane 1:1) Rf 0.43
Mass spectrum MH^+ 274

Example 21

2-Methylpropionic acid [3-(2,3-dihydro-benzofuran-4-yl)-propyl]-amide

The compound was prepared by the method described in Example 19 using 2-methylpropionyl chloride (0.05ml) to give the title compound as a white solid (93mg).
Tlc SiO_2 (Ethyl acetate / hexane 1:1) Rf 0.35
Mass spectrum MH^+ 248

Example 22

Propionic acid [3-(2,3-dihydro-benzofuran-4-yl)-propyl]-amide

The compound was prepared by the method described in Example 19 using propionyl chloride (0.044ml) to give the title compound as a white solid (71mg).
Tlc SiO_2 (Ethyl acetate / hexane 1:1) Rf 0.22
Mass spectrum MH^+ 234

Example 23

Butyric acid [3-(2,3-dihydro-benzofuran-4-yl)-propyl]-amide

The compound was prepared by the method described in Example 19 using butyryl chloride (0.05ml) to give the title compound as a white solid (67mg).
Tlc SiO_2 (Ethyl acetate / hexane 1:1) Rf 0.27
Mass spectrum MH^+ 248

Example 24

Cyclopropanecarboxylic acid [3-(2H-chromen-7-yl)-propyl]-amide (A) and Cyclopropanecarboxylic acid [3-(2H-chromen-5-yl)-propyl]-amide (B)

A solution of cyclopropanecarboxylic acid [3-(3-prop-2-ynyloxy-phenyl)-propyl]-amide (415mg) in N,N-diethylaniline (2ml) was heated at 215°C for 24h. The cooled mixture was purified by column chromatography on silica. Elution with hexane / ethyl acetate 3:1 gave the title compound (A) as a colourless solid (16mg)

Mass spec Found MH^+ 258
Tlc SiO_2 (Hexane / ethyl acetate 2:1) Rf 0.27

and the title compound (B) as a colourless oil (79mg)

Mass spec Found MH^+ 258
Tlc SiO_2 (Hexane / ethyl acetate 2:1) Rf 0.23

Example 25

Cyclopropanecarboxylic acid (3-chroman-5-yl-propyl)-amide

A solution of cyclopropanecarboxylic acid [3-(2H-chromen-5-yl)-propyl]-amide (76mg) in ethanol (5ml) was hydrogenated over platinum (5% on carbon, 10mg) for 16h. The catalyst was filtered off and the filtrate evaporated. The residue was purified by column chromatography on silica. Elution with hexane / ethyl acetate 2:1 gave the title compound as a colourless solid (56mg)

Mass spec Found MH^+ 260.2

TLC SiO_2 (Hexane / ethyl acetate 2:1) Rf 0.23

Example 26

N-[3-[2,3-Dihydro-5-fluorobenzofuran-4-yl]propyl]acetamide

A solution of the E- and Z-3-[5-fluororobenzofuran-4-yl]acrylonitriles (0.5g) in acetic acid (20ml) and acetic anhydride (1.25ml) containing 10% palladium on charcoal (50mg; 50% wet paste) and 5% platinium on charcoal (50mg) was hydrogenated at 150psi and 75° for 3 days. The solution was filtered through hyflo and evaporated to dryness and the residue purified by chromatography (Biotage Flash 40; 90g; ethyl acetate:hexane 1:1 then changing to ethyl acetate) to give an impure sample of the title compound contaminated with N-[3-[4-fluorobenzofuran-4-yl]propyl]acetamide. This material was combined with a similar product obtained from an identical reaction and subjected to further hydrogenation in acetic acid (25ml) containing 10% palladium on charcoal (50mg; 50% wet paste) and 5% platinium on charcoal (50mg) at 170psi and 75° for 24h. The solution was filtered and evaporated and the residue dissolved in dichloromethane and washed with 4% sodium bicarbonate, dried and evaporated to give the title compound (0.68g) as an oil.

Tlc (Ethyl acetate) Rf 0.27
Mass spectrum MH^+ 238

Example 27

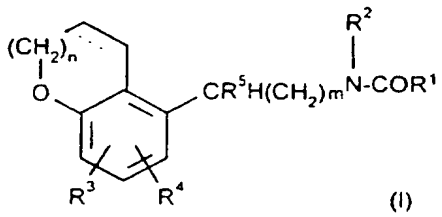
Cyclopropane carboxylic acid [3-(2,3-dihydro-5-fluorobenzofuran-4-yl)propyl]-amide

3-(2,3-Dihydro-5-fluorobenzofuran-4-yl)propylamine hydrochloride (0.27g) in dichloromethane (5ml) containing triethylamine (0.5ml) was cooled in ice. Cyclopropanecarbonyl chloride (0.12ml) was added and stirring continued at 5° for 2h and at room temperature for 16h The mixture was washed with water and passed through a solid phase extraction cartridge using ethyl acetate/hexane (1:1) to give the title compound as a white solid (0.21g).

Tlc (Ethyl acetate/hexane 1:1) Rf 0.25
Mass spectrum MH^+ 263

Claims

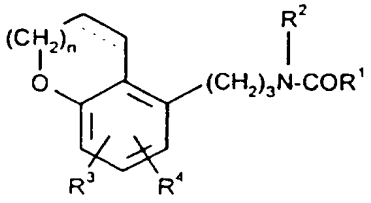
1. A compound of formula (I)



(I)

wherein R^1 and R^2 which may be the same or different represent H, C_{1-6} alkyl, C_{3-7} cycloalkyl or aryl;
R^3, and R^4 which may be the same or different represent H, halogen, C_{1-6} alkyl; or substituted aryl
R^5 represents H or C_{1-6} alkyl or;
n is an integer 0, 1 or 2
and m is an integer 1, 2, 3, or 4;
the dotted line indicates the presence or absence of an additional bond;
and pharmaceutically acceptable solvates thereof.

2. A compound of formula (Ia)



(1a)

wherein R^1 and R^2 which may be the same or different represent H, C_{1-6} alkyl or substituted alkyl, C_{3-7} cycloalkyl or aryl;
R^3 and R^4 which may be the same or different represent H, halogen or C_{1-6} alkyl;
n is an integer 0,1 or 2
the dotted line indicates the presence or absence of an additional bond; and pharmaceutically acceptable solvates thereof.

3. A compound according to claim 1 or 2 wherein R^3 and R^4 are hydrogen, halogen and C_{1-3} alkyl.

4. A compound according to claim 3 wherein the halogen is chlorine and/or fluorine.

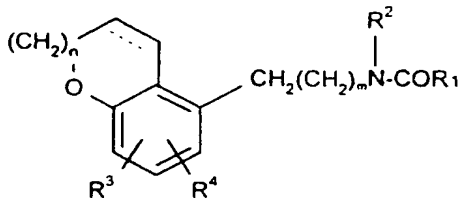
5. A compound according to claim 1 or 2 wherein R^1 and R^2 are hydrogen, C_{1-3} alkyl or C_{3-5} cycloalkyl.

6. A compound according to claim 5 wherein R^1 is methyl or cyclopropyl.

7. A compound according to claim 6 wherein at least one of R^1 and R^2 are hydrogen.

8. A compound according to any preceding claim wherein n is zero.

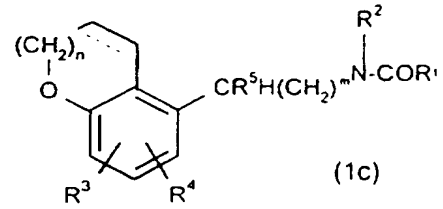
9. A compound of formula 1(b)



(1b)

wherein R^1 and R^2 which may be the same or different represent H, C_{1-6} alkyl or substituted alkyl, C_{3-7} cycloalkyl or aryl;
R^3, and R^4 which may be the same or different represent H, halogen, or C_{1-6} alkyl or substituted aryl;
n is an integer 0, or 1
and m is an integer 2, 3, 4 or 5;
the dotted line indicates the presence or absence of an additional bond;
and pharmaceutically acceptable solvates (e.g. hydrates) thereof.

10. A compound of formula 1(c)



(1c)

wherein R^1 and R^2 which may be the same or different represent H, C_{1-6} alkyl or C_{3-7} cycloalkyl;
R^3, and R^4 which may be the same or different represent H, halogen, or C_{1-6} alkyl;
R^5 is H or C_{1-6} alkyl;
n is an integer 0, or 1
and m is an integer 1, 2, 3, or 4;
the dotted line indicates the presence or absence of an additional bond;
and pharmaceutically acceptable solvates (e.g. hydrates) thereof.

11. N-[3-(2,3-dihydro-benzofuran-4-yl)-propyl]acetamide,
Cyclopropanecarboxylic acid -[3-(2,3-dihydro-benzofuran-4-yl)-propyl]-amide,
Cyclopropanecarboxylic acid -[3-(5-chloro-2,3-dihydro-benzofuran-4-yl)propyl]amide,
Cyclopropanecarboxylic acid -[3-(5-chloro-7 fluoro-2,3-dihydro-benzofuran-4-yl)propyl]-amide,
Cyclopropanecarboxylic acid [3-(5-chloro-7-fluoro-benzofuran-4-yl)-propyl]-amide,
Cyclopropanecarboxylic acid -[3-benzofuran-4-yl)-propyl]-amide,
Cyclopropanecarboxylic acid (3-chroman-5-yl-propyl)-amide.
N-[3-(2,3-dihydro-5-fluorobenzofuran-4-yl)propyl]acetamide,
Cyclopropane carboxylic acid [3-(2,3-dihydro-5-benzofuran-4-yl)propyl]amide.

12. A pharmaceutical formulation comprising a compound of formula (I) according to any of claims 1 to 11 together with one or more pharmaceutically acceptable carriers therefor.

13. A process of preparing a pharmaceutical formulation comprising a compound of formula (I) according to any of claims 1 to 11 together with one or more pharmaceutically acceptable carriers therefor, which process comprises mixing said compound of formula (I) together with said one or more pharmaceutically acceptable carriers therefor.

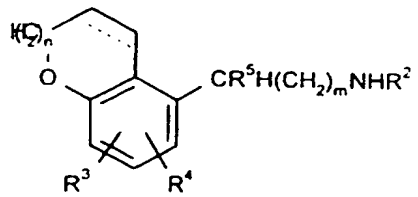
14. A compound of formula (I) according to claims 1 to 11 for use in therapy.

15. A compound of formula (I) according to any of claims 1 to 11 for use in the preparation of a medicament for use in the treatment of conditions associated with a disturbed functioning of systems regulated by melatonin.

16. A method of treating a mammal, including man, comprising administration of an effective amount of a compound of formula (I) according to any of claims 1 to 11, for the treatment of conditions associated with a disturbed functioning of systems regulated by melatonin.

17. A process for the preparation of a compound of formula (I) according to any of claims 1-11 which process comprises

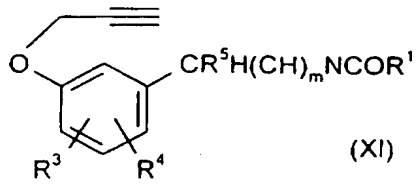
(A) acylation of a compound of formula (II).



(II)

or

(B) cyclisation of a compound of formula (XI)



(XI)

18. Compounds of formulae (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII) and (XVIII)..

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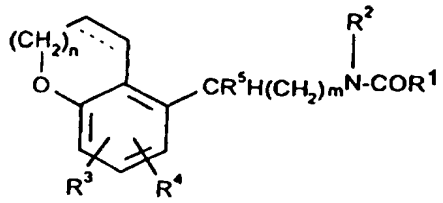
(74) Agent: LEAROYD, Stephanie, Anne; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(54) Title: BENZOFURANS AND BENZOPYRANS AS CHRONOBIOLOGICAL AGENTS

(57) Abstract

A compound of formula (I), wherein R^1 and R^2 which may be the same or different represent H, C_{1-6} alkyl, C_{3-7} cycloalkyl or aryl; R^3, and R^4 which may be the same or different represent H, halogen, C_{1-6} alkyl; or substituted aryl; R^5 represents H or C_{1-6} alkyl or; n is an integer 0, 1 or 2 and m is an integer 1, 2, 3 or 4; the dotted line indicates the presence or absence of an additional bond; and pharmaceutically acceptable solvates thereof.



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INTERNATIONAL SEARCH REPORT

Inte. ional Application No
PCT/EP 97/02402

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D307/79 C07D311/04 A61K31/35

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	M. F. SEMMELHACK ET AL.: "New substitution reactions on indole promoted by the Cr(CO)3 unit" J. ORGANOMET. CHEM., vol. 240, no. 1, 1982, pages C5-C10, XP002042868 * page C7: compounds of formula C-4-B, C-4-F * ---	18
X	R. BENASSI ET AL.: "Conformational Analysis of Organic Carbonyl Compounds. Part 4. A 1H and 13C Nuclear Magnetic Resonance Study of Formyl and Acetyl Derivatives of Benzo[b]furan" J. CHEM. SOC., PERKIN TRANS. 2, no. 9, - 1984 pages 1479-1485, XP002042869 * compound of formula 3b * --- -/--	18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
8 October 1997	16. 01. 98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Herz, C

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	R. L. DORTA ET AL.: "Serendipitous Acid-Catalyzed Rearrangement of 13-Methoxy-1,6,8-trioxadispiro[4.1.5.3]pentadecane to 3-Chroman-5-yl-1-ol" J. ORG. CHEM., vol. 62, no. 7, 1997, pages 2273-2274, XP002042870 * compound of formula 5 *	18
A	G. ECKER ET AL.: "Improved Synthesis and Pharmacologic Activity of the Enantiomers of a New Benzofurane Type Antiarrhythmic Compound" CHIRALITY, vol. 6, no. 4, 1994, pages 329-336, XP002042871 * entire document *	1-18
A	G. ECKER ET AL.: "Synthese und Pharmakodynamische Aktivität von 2-(3-(2-Phenylethyl)benzofuran-2-yl)-N-propyl-ethanamin" ARCH. PHARM. (WEINHEIM, GER.), vol. 328, no. 4, 1995, pages 343-348, XP002042872 * entire document *	1-18
A	WO 93 12754 A (ABBOTT LABORATORIES) 8 July 1993 see page 3, line 15 - line 29; claims 1-13	1-18
A	WO 92 17464 A (C. R. NOE, W. FLEISCHHACKER) 15 October 1992 see claims 1-19	1-18
A	EP 0 042 299 A (KOWA COMPANY, LTD.) 23 December 1981 see page 12, line 8 - line 26; claims 1-5	1-18

3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 97/02402

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Claims 1-17, 18 (part)
Claim 18 (part)
Claim 18 (part)

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Claims 1 - 17, 18 (part)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inte. ional Application No
PCT/EP 97/02402

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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